

present in the query sequence, as well as a modified ("masked") version of the query sequence in which all the annotated repeats have been masked (e.g., replaced by Ns). The RepeatMasker program is publicly available (see, e.g., the website at repeatmasker.genome.washington.edu/).

⌈ Please amend the paragraph bridging pages 7-8 of the application as follows: ⌋

Other usable programs include Censor (Jurka, *et al.* (1996) *Computers and Chemistry* 20:119-122; see, e.g., the website at girinst.org/Censor_Server.html; Genetic Information Research Institute, California); Satellites or Repeats (Institut Pasteur, Paris; see, e.g., the website at bioweb.pasteur.fr/seqanal/interfaces); and others.

B1
Censor

Please amend the last full paragraph on page 9 of the application as follows:

Typically, the masked sequence (*i.e.*, collection of selected subsequences) will be compared with the genome database using a suitable algorithm such as BLAST (see, e.g., the BLAST server at the National Center for Biotechnology Information). A BLAST or equivalent search will identify sequences within the genome that are homologous to the masked sequence, preferably ranked in order of similarity to each subsequence.

B2

Please amend the paragraph bridging pages 10-11 of the application as follows:

A preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, *Nuc. Acids Res.* 25:3389-3402 (1997) and Altschul *et al.*, *J. Mol. Biol.* 215:403-410 (1990), respectively. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is

B3

publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W , T , and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, $M=5$, $N=-4$ and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, $M=5$, $N=-4$, and a comparison of both strands.

Please amend the paragraph bridging pages 12-13 of the application as follows:

Typically, the primers will be designed not only based on the size of the product, but also taking into account any of a large number of considerations for optimal primer design, *e.g.*, to exclude potential secondary structures within the primers, with a desired T_m (that is preferably similar for each member of a pair of primers), to include

additional sequences such as restriction sites to facilitate cloning of the amplified product, etc. Examples of suitable programs for designing (and analyzing potential primer sequences) include, but are not limited to, Primer3 (from the Whitehead Institute; website at genome.wi.mit.edu/cgi-bin/primer/primer3.cgi, PrimerDesign website at chemie.uni-marburg.de/~becker/pdhome.html Primer Express® Oligo Design Software (PE Biosystems), DOPE2 (Design of Oligonucleotide Primers website at dope.interactiva.de/); DoPrimer (website at doprimer.interactiva.de); NetPrimer (website at premierbiosoft.com/netprimer.html); Oligos-U-Like--Primers3 (website at path.cam.ac.uk/cgi-bin/primer3.cgi); Oligo (v5.0); CpG Ware™ Primer Design Software, PrimerCheck (website at chemie.uni-marburg.de/~becker/freeware/freeware.html#primercheck), and others. General parameters for designing primers can be found in any of a large number of resources and publications, including Dieffenbach, *et al.*, in PCR Primer, A Laboratory Manual, Dieffenbach *et al.*, Ed., Cold Spring Harbor Laboratory Press, New York (1995), pp.133-155; Innis, *et al.*, in PCR protocols, A Guide to Methods and Applications, Innis, *et al.*, Ed., CRC Press, London (1994), pp. 5-11; Sharrocks, in PCR Technology, Current Innovations, Griffin, H.G., and Griffin, A.M, Ed., CRC Press, London (1994) 5-11.

IN THE CLAIMS:

Please ~~cancel~~ claim 39.

Please amend claims 11-12 and 27-28 and add new claims 40-42 as follows:

11. (Once Amended) The method of claim 1, wherein said first process is executed using [Repeat Masker software] a software program that screens sequences for:

- i. interspersed repeats that are known to exist in mammalian genomes and;
- ii. low complexity DNA sequences.

Nic.
Amend
with
Appendix
B.